(FILE 'HOME' ENTERED AT 13:33:55 ON 21 JUL 2001)

FILE 'MEDLINE, CAPLUS, EMBASE' ENTERED AT 13:34:09 ON 21 JUL 2001

L1	73	S RESTIN
L2	10	S L1 AND ANGIOGEN?
L3	9	DUP REMOVE L2 (1 DUPLICATE REMOVED)

L3 ANSWER 1 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001149119 EMBASE
TITLE: Endogenous **angiogenesis** inhibitors and their therapeutic implications.

AUTHOR: Cao Y.
CORPORATE SOURCE: Y. Cao, Laboratory of Angiogenesis Research, Microbiology and Tumor Biology Ctr., Karolinska Institute, S-171 77 Stockholm, Sweden. yihai.cao@mtc.ki.se

SOURCE: International Journal of Biochemistry and Cell Biology, (2001) 33/4 (357-369).
Refs: 88
ISSN: 1357-2725 CODEN: IJBBFU

PUBLISHER IDENT.: S 1357-2725(01)00023-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
036 Health Policy, Economics and Management
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis models. While many of these **angiogenesis** inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and serpin antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of these specific endothelial inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological **angiogenesis**, but may also provide an important therapeutic strategy for the treatment of cancer and other **angiogenesis** dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these **angiogenesis** inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic gene therapy, improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location, and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other **angiogenesis** dependent diseases. .COPYRGT. 2001 Elsevier Science Ltd.

L3 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:34763 CAPLUS
DOCUMENT NUMBER: 132:98141
TITLE: Methods of inhibiting proliferative diseases by inhibiting TGF.beta.-mediated **angiogenesis**

INVENTOR(S): Sukhatme, Vikas P.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, [redacted] GE, GR, IE, IT, LU, MC, NL, [redacted] SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, [redacted]

AU 9950877 A1 20000124 AU 1999-50877 19990701

PRIORITY APPLN. INFO.: US 1998-91829 P 19980706
WO 1999-US14981 W 19990701

AB Disclosed are methods of inhibiting proliferative diseases characterized by TGF.beta.-mediated **angiogenesis** e.g. clear-cell renal carcinoma (RCC). Elevated TGF-.beta.1 in RCC stimulates **angiogenesis**. Antagonizing TGF-.beta. activity with neutralizing antibody against TGF-.beta. provides methods of inhibiting **angiogenesis** and RCC tumor growth. It is further shown that TGF-.beta.1 is target for the von Hippel-Lindau tumor suppressor protein (pVHL). Repression of TGF-.beta. messages occurs predominantly at post-transcriptional level.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Ananth, S; CANCER RESEARCH 1999, V59(9), P2210 CAPLUS
(2) Marzo, A; CANCER RESEARCH 1997, V57(15), P3200 CAPLUS
(3) Stiles, J; JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY 1997, V56(4), P435 CAPLUS
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L3 ANSWER 3 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000331436 EMBASE
TITLE: Progress in antiangiogenic gene therapy of cancer.
AUTHOR: Feldman A.L.; Libutti S.K.
CORPORATE SOURCE: Dr. S.K. Libutti, Surgery Branch, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, United States
SOURCE: Cancer, (15 Sep 2000) 89/6 (1181-1194).
Refs: 147
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB BACKGROUND. Because tumors require **angiogenesis** for growth, inhibiting **angiogenesis** is a promising strategy for treating cancer patients. Although numerous endogenous **angiogenesis** inhibitors have been discovered, the clinical evaluation of these agents has been hindered by high dose requirements, manufacturing constraints, and relative instability of the corresponding recombinant proteins. Therefore the delivery of these proteins using gene therapy has become increasingly attractive. METHODS. Based on their own antiangiogenic gene therapy research, the authors evaluated the published experience with antiangiogenic gene therapy models using the National Library of Medicine's PubMed search service and the reference lists of the publications cited. RESULTS. Greater than 40 endogenous inhibitors of **angiogenesis** have been characterized. Thirteen have been employed in gene therapy models, all of which showed antitumor activity in experimental animals. Other approaches have inhibited the expression or activity of proangiogenic cytokines such as vascular endothelial growth factor. The ideal gene delivery vector would target tumor tissue preferentially to minimize systemic toxicity of the transgene product. However, the low toxicity profile of endogenous inhibitors of **angiogenesis** has allowed the success of systemic antiangiogenic gene therapy in a number of preclinical models, in which normal host tissues act as a 'factory' to produce high circulating concentrations of antiangiogenic proteins. CONCLUSIONS. Difficulties with the large-scale use of antiangiogenic agents have hindered their investigation in clinical trials. Antiangiogenic gene therapy offers the potential for cancer patients to manufacture their own antiangiogenic proteins. This strategy has been increasingly successful in preclinical models and represents an exciting new approach to cancer therapy. (C) 2000 American Cancer Society.

L3 ANSWER 4 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

FILE SEGMENT: 023 Urology and Nephrology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Research during the past few years has contributed vastly to a better understanding of fibrosis and **angiogenesis**. Although studies to understand the molecular processes associated with fibrosis and **angiogenesis** were performed independently of each other, some common parallels have emerged. Translation of these observations into potential therapeutic possibilities needs further exploration. (C) 2000 Lippincott Williams and Wilkins.

L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:388310 CAPLUS
DOCUMENT NUMBER: 131:40546
TITLE: Methods of producing anti-**angiogenic** proteins: endostatin, angiostatin or **restin**, using a Pichia yeast expression system
INVENTOR(S): Sukhatme, Vikas P.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929878	A2	19990617	WO 1998-US25892	19981208
WO 9929878	A3	19990916		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9918065	A1	19990628	AU 1999-18065	19981208
EP 1038011	A2	20000927	EP 1998-962932	19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:
US 1997-67883 P 19971208
US 1998-82663 P 19980422
US 1998-108536 P 19981116
WO 1998-US25892 W 19981208

AB Methods for making proteins with anti-**angiogenic** properties are disclosed, including angiostatin, endostatin, and **restin**. The system used is a yeast expression system which produces biol. active proteins at high titer, specifically the Pichia pastoris yeast expression system. In particular, the pPICZ.alpha.A plasmid vector is provided which contains a multiple cloning site with a His.Tag motif. Biol. activity is evaluated by endothelial cell migration, tumor growth inhibition in mammalian systems, arrest of endothelial cell in G1 phase of the cycle cycle, and induction of apoptosis in endothelial cells. The anti-**angiogenic** proteins produced by the described methods exhibit superior biol. activity to anti-**angiogenic** proteins produced by other expression methods, and biol. active protein is typically produced at concns. of about 10-20 mg/L of culture medium.

L3 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:388268 CAPLUS
DOCUMENT NUMBER: 131:39759
TITLE: **Restin** and apomigren fragments of human collagen type XV .alpha.1 chain and their anti-**angiogenic** activities
INVENTOR(S): Sukhatme, Vikas P.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9918038 A1 19990628 AU 1999-18088 19981208
EP 1037985 A1 20000927 EP 1998-966966 19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-67888 P 19971208
US 1998-82663 P 19980422
US 1998-106836 P 19981116
WO 1998-US26058 W 19981208

AB The invention relates to **restin**, a novel anti-**angiogenic** protein is described, as well as its fragment, designated apomigren. **Restin** is a proteolytic fragment of the C-terminal fragment of the NC1 domain of the alpha1 chain of human collagen type XV. Apomigren is a fragment of **restin**, and comprises the C-terminal 85 residues of **restin**,. Methods for expression of the proteins at high titer are also described. **Restin** inhibits the migration of endothelial cells in vitro and suppresses the growth of tumors in a xenograft renal carcinoma model. Apomigren has anti-**angiogenic** activity equal or superior to that of endostatin.

REFERENCE COUNT: 6
REFERENCE(S): (1) Bachelot; Proceedings of the 89th Annual Meeting of the American Association for Cancer Research 1998, V39, P271
(2) Childrens Medical Center; WO 9715666 A 1997 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:388297 CAPLUS
DOCUMENT NUMBER: 131:41277
TITLE: Mutants of endostatin, "em 1" having anti-**angiogenic** activity and methods of use thereof
INVENTOR(S): Sukhatme, Vikas P.
PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929855	A1	19990617	WO 1998-US26157	19981208
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917180	A1	19990628	AU 1999-17180	19981208
EP 1037989	A1	20000927	EP 1998-966016	19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-67888 P 19971208
US 1998-82663 P 19980422
US 1998-106836 P 19981116
WO 1998-US26057 W 19981208

AB Described herein are novel mutants of endostatin, one of which, designated "EM 1", has anti-**angiogenic** activity similar or superior to that of wild type endostatin. The invention relates to the discovery of an

REFERENCE COUNT: 8
REFERENCE(S): (1) Boehm, T; Biochemical and Biophysical Research Communications 1998, V252, P190 CAPLUS
(2) Dhanabal, M; Cancer Research 1999, V59, P189 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 1999:134199 CAPLUS
DOCUMENT NUMBER: 130:332418
TITLE: Antiangiogenic Activity of **Restin**, NC10 Domain of Human Collagen XV: Comparison to Endostatin
AUTHOR(S): Ramchandran, Ramani; Dhanabal, Mohanraj; Volk, Ruediger; Waterman, Matthew J. F.; Segal, Mark; Lu, Hua; Knebelmann, Bertrand; Sukhatme, Vikas P.
CORPORATE SOURCE: Renal Div., Dep. Med., Beth Israel Deaconess Med. Cent., Harvard Med. Sch., Boston, MA, 02215, USA
SOURCE: Biochem. Biophys. Res. Commun. (1999), 255(3), 735-739
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on a homol. search with endostatin, the C-terminus 185 aa of collagen XVIII, the authors report the cloning, expression, and antiangiogenic activity of a 22 kDa human collagen XV fragment, that the authors have named **restin**. **Restin** was expressed in the prokaryotic pET expression system. The authors have shown that **restin** inhibits the migration of endothelial cells in vitro but has no effect on the proliferation of these cells. A polyclonal antibody raised against endostatin cross-reacted with **restin**. Systemic administration of **restin** suppressed the growth of tumors in a xenograft renal carcinoma model. (c) 1999 Academic Press.
REFERENCE COUNT: 13
REFERENCE(S): (1) Angiolillo, A; J Exp Med 1995, V182, P155 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000035788 EMBASE
TITLE: **Angiogenesis** inhibitors. New anticancer strategy.
AUTHOR: Zgodzinski W.; Wallner G.; Dabrowski A.
CORPORATE SOURCE: W. Zgodzinski, 2nd Department of General Surgery, Univ. School of Medicine in Lublin, Staszica 16, PL 20-081 Lublin, Poland
SOURCE: Polish Journal of Pharmacology, (1999) 51/6 (455-462). Refs: 47
ISSN: 1230-6002 CODEN: PJPAE3
COUNTRY: Poland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Neoangiogenesis has been proved to be crucial in neoplasmatic tumor growth and metastases. Over the last few years, the factors that have both a positive (**angiogenic**) and negative (antiangiogenic) influence on tumor growth have been identified. The potential use of natural and synthetic factors that suppress vasculature formation as anticancer drugs is currently under intense investigation. Recently, several antiangiogenic compounds, including TNP-470 or matrix metalloproteinase inhibitors, have